Angiotensin-Converting Enzyme (ACE, I/D) Gene Polymorphism and Susceptibility to Abdominal Aortic Aneurysm or Aortoiliac Occlusive Disease

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Background. The purpose of this study was to examine the role of polymorphism in angiotensin converting enzyme gene (ACE, I/D) in the development of abdominal aortic aneurysm (AAA) or aortoiliac occlusive disease (AIOD).

Materials and methods. We investigated 829 individuals in 4 groups: AAA (n = 133), AIOD (n = 152), control (n = 152), and a random Polish population group (n = 392). ACE I/D gene polymorphism analysis was performed by polymerase chain reaction and gel electrophoresis. The genotype distribution was in Hardy-Weinberg equilibrium.

Results. The genotype distribution and allele frequency of ACE I/D were not significantly different between patients with AAA or AIOD and the control or the population group. Significant differences were found between the following groups: 1) hypertensive patients with AAA and normotensive patients with AAA (OR = 3.08 95% CI 1.22–7.79, P = 0.0147); 2) hypertensive patients with AAA and the population group (OR = 2.56; 95% CI 1.27–5.16, P = 0.0066). Since the majority of subjects were male, these associations were also true when only male hypertensive subjects with AAA were compared with male normotensive patients with AAA or to male population group. No relation of the ACE gene polymorphism to hypertension in the AIOD group was found.

Conclusions. ACE I/D gene polymorphism is not a susceptibility factor to aortoiliac occlusive disease; however it may be an important factor in the development of AAA when coexisting with hypertension. © 2009 Elsevier Inc. All rights reserved.

Key Words: ACE polymorphism; abdominal aortic aneurysm; aortoiliac occlusive disease; genetic risk factors; hypertension.

INTRODUCTION

Abdominal aortic aneurysm (AAA) is a life threatening chronic condition affecting approximately 1% to 6% of the population in developed countries [1–3]. Pathogenesis of AAA is considered to be a multifactorial process with both genetic and environmental risk factors [4, 5]. Abdominal aortic aneurysms are characterized by histological signs of chronic inflammation, destruction of elastin and collagen in the media and adventitia, smooth muscle cell depletion with thinning of the medial wall, and neovascularization [1–3, 6].

AAA is frequently associated with atherosclerosis, although it is not a necessary factor to generate aneurysm [7]. The infrarenal aorta is prone to both aneurysmal disease and occlusive atherosclerosis. Aortoiliac occlusive disease (AIOD) is a symptom of systemic atherosclerosis localized in the distal segment of abdominal aorta (below the renal arteries) and frequently extending to the iliac arteries. AIOD, as an atherosclerotic disease, has a complex pathogenesis and is frequent in developed countries. Both AAA and AIOD have common risk factors (e.g., smoking and dyslipidemia) and share some similarities like metalloproteinases expression and smooth muscle cell apo-
ptosis [8], but the exact mechanisms underlying these pathologies of abdominal aorta are not known.

Since the first report in 1992 by Cambien et al. [9] on the association of angiotensin-converting enzyme (ACE I/D) gene polymorphism with coronary arterial disease and myocardial infarction (MI) many investigations have focused on the relationship between this polymorphism and cardiovascular disease, restenosis, hypertension, and other diseases (for review see [10, 11]). ACE levels in plasma and tissue are under genetic control [12, 13]. Rigat et al. found that approximately 50% of ACE plasma level variability was associated with I/D gene polymorphism [12]. ACE D allele carriers have higher ACE plasma [12, 13] and tissue [14] levels compared with those with ID and II genotypes. It is believed that I allele may have a silencing effect resulting in the production of angiotensin II with a dose-dependent effect (the mean plasma concentration of ACE in DD homozygotes is approximately twice higher than that of II homozygotes whereas ID individuals have intermediate ACE concentrations) [12]. An increased ACE plasma level affects the angiotensin II plasma levels, which may lead to the remodeling of the vascular tissue and atherosclerosis [15]. Experimental animal model studies showed a relationship between angiotensin II, atherosclerosis, and aortic aneurysm formation [16]. In aneurysmal aorta, significantly increased levels of the angiotensin II-forming enzymes, ACE and chymase, were found [17]. All these observations could support a potential role of ACE gene polymorphism in the development of AAA or AIOD.

Thus far, conflicting results concerning the ACE gene polymorphism and risk of abdominal aortic aneurysm were reported [18–20]. To the best of our knowledge, no data regarding the determination of ACE gene polymorphism in patients affected with AIOD were reported.

The aim of this study was to examine the potential impact of the insertion/deletion ACE gene polymorphism on the susceptibility to develop the abdominal aortic aneurysm or aortoiliac occlusive disease. Additionally, the effect of the traditional risk factors for the development of these pathologies was compared.

MATERIALS AND METHODS

Subjects

The study included consecutive patients with either AAA (n = 133) or AIOD (n = 152) referred to and subjected to surgery in the Department of Vascular Surgery of the Poznan University of Medical Sciences in the years 2003 to 2006. AAA was defined as a focal dilation of the abdominal aorta at least 50% larger than the adjacent suprarenal segment (for review see [1]). Familial AAA cases and patients with aneurysm characterized by inflammation, dissection, or emerged as a result of trauma were excluded from the study. Aortoiliac occlusive disease was defined as a chronic atherosclerotic occlusion of distal segments of aorta and iliac arteries. The AIOD group included patients with clinical symptoms of ischemia in III and IV degree (Fontaine’s) diagnosed by both anatomical ad symptomatic criteria.

Controls (n = 152) comparable for age and gender were recruited from in-patients and out-patients admitted to the hospital for reasons other than AAA or AIOD, with neither history of AAA nor of AIOD and confirmed to be free from these diseases.

All studied individuals underwent complete clinical examination to exclude subjects suffering from symptoms of any inflammatory or neoplastic diseases as well as those with lung emphysema, formation of cysts, or cystomas in parenchymatosous organs. Chronic renal failure or cerebrovascular disease were also disqualifying criteria from the study (to avoid interference with potential association of the ACE gene polymorphism with these diseases). Data concerning medical records, medication history and smoking habit were collected based on detailed questionnaire. Lipid fractions were measured after overnight fasting.

All subjects underwent Doppler ultrasound scanning examination. Aortic diameter was measured below the origin of renal arteries. Patients with AAA or AIOD were subjected to further examinations by digital subtraction angiography or computed tomography angiography. The subjects were considered as hypertensives when they had diastolic pressure above 90 mm Hg or systolic pressure above 140 mm Hg or were on antihypertensive therapy. Dyslipidemia was defined according to the Third Report of the National Cholesterol Education Program (NCEP-III) [21].

Since in genetic association studies population background is very important, 392 samples of a random Polish population group were collected as an additional reference. The population group was an auxiliary group used in analysis to compare the distribution of the ACE (I/D) gene polymorphism in general Polish population. These samples originated from our DNA bank with no clinical data available but age and gender. Our DNA bank was composed of volunteers who were healthy at the moment of blood collection. The DNA samples were randomly selected from the DNA bank only to match male/female ratio. The group was composed of 75% males and 25% females, mean age 40.1. All 829 subjects of the present study were Caucasians from middle-west Poland.

The research protocol was reviewed and approved by the institutional ethics committee and informed consent from the patients and control subjects was obtained.

Detection of ACE Polymorphism

DNA was isolated from 5 mL of peripheral blood samples by standard methods. The ACE gene polymorphism was estimated based on polymerase chain reaction (PCR) amplification of a single fragment of intron 16 according to Rigat et al. [22]. PCR products corresponding to (I) insertion (480 bp) or (D) deletion (193 bp) allele were analyzed on 1.5% agarose gel stained with ethidium bromide. Since the D allele in heterozygous sample may be preferentially amplified, each sample evaluated as the DD genotype was subjected to a second independent PCR amplification at an annealing temperature of 67°C with a primer pair recognizing an insertion specific region (hace5a: 5’ TGGGACCACAGCGCCCGCCACTAC 3’; hace5c: 5’ TCGCCAGCCCTCCATGGCCTATA 3’) [23]. The PCR product of 335 bp was amplified only in the presence of I allele (in the case of heterozygote) whereas there was no product in samples homozygous for D allele.

Statistical Analysis

Statistical analysis was performed using Statistica software (StatSoft Polska, Krakow, Poland) version 6.0. Demographic and clinical data were expressed as mean ± SD, median, and range. Genotype and allele frequencies were obtained by direct count. Consistency with Hardy-Weinberg rule and the differences between the groups were assessed by two-tailed $\chi^2$ test with 95% CI. Two models of inheritance, recessive (DD versus ID + II) and dominant (DD + ID versus II), were tested. The nonparametric Mann-Whitney test, $\chi^2$ test, and exact Fisher test were used. For a comparison of the traditional risk factors (hypertension, smoking habit, dyslipidemia,
BMI) and age and gender between AAA and AIOD in association with the ACE I/D gene polymorphism a multivariate logistic regression analysis was performed. The odds ratio (OR) with a 95% CI was determined. A P-value < 0.05 was considered to indicate statistical significance. All tests were two-tailed.

RESULTS

Demographic and clinical characteristics of the patients and controls covered by the study are presented in Table 1. The ACE genotype distribution and allele frequencies were in Hardy-Weinberg equilibrium and are described in Table 2. No significant differences in genotype distribution and allele frequencies between patients with the AAA or AIOD and the control or population groups were observed (neither in dominant nor in recessive model of inheritance). However, when the genotype distributions of the AAA, AIOD, and control groups were analyzed in relation to blood pressure

<table>
<thead>
<tr>
<th>Variable</th>
<th>AAA (n = 133)</th>
<th>AIOD (n = 152)</th>
<th>Control (n = 152)</th>
<th>P value AAA versus Control</th>
<th>P value AIOD versus Control</th>
<th>P value AAA versus AIOD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>84.2%</td>
<td>77.0%</td>
<td>75.0%</td>
<td>0.0555</td>
<td>0.6871</td>
<td>0.1250</td>
</tr>
<tr>
<td>Female</td>
<td>15.8%</td>
<td>23.0%</td>
<td>25.0%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (y) mean ± SD</td>
<td>68.0 ± 8.2</td>
<td>59.4 ± 8.2</td>
<td>61.4 ± 11.8</td>
<td>&lt;0.0001</td>
<td>0.0255</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age (y) median (min-max)</td>
<td>69.0 (45–92)</td>
<td>58.0 (42–80)</td>
<td>63.0 (34–91)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²) mean ± SD</td>
<td>27.0 ± 3.8</td>
<td>25.0 ± 4.4</td>
<td>27.0 ± 3.0</td>
<td>0.1446</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BMI (kg/m²) median (min-max)</td>
<td>26.6 (17.8–45.0)</td>
<td>24.2 (13.0–37.6)</td>
<td>27.0 (18.0–35.7)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol (mmol/L) mean ± SD</td>
<td>5.5 ± 1.3</td>
<td>5.6 ± 1.3</td>
<td>5.3 ± 1.9</td>
<td>0.3773</td>
<td>0.9470</td>
<td>0.3738</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L) median (min-max)</td>
<td>5.3 (2.6–10.8)</td>
<td>5.5 (2.2–11.3)</td>
<td>5.7 (0.6–9.1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDL-cholesterol (mmol/L) mean ± SD</td>
<td>1.2 ± 0.3</td>
<td>1.2 ± 0.5</td>
<td>1.3 ± 0.3</td>
<td>0.0001</td>
<td>0.0006</td>
<td>0.5461</td>
</tr>
<tr>
<td>HDL-cholesterol (mmol/L) median (min-max)</td>
<td>1.1 (0.4–2.1)</td>
<td>1.2 (0.4–4.9)</td>
<td>1.3 (0.6–2.9)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL-cholesterol (mmol/L) mean ± SD</td>
<td>3.4 ± 1.1</td>
<td>3.4 ± 1.1</td>
<td>3.5 ± 1.1</td>
<td>0.4672</td>
<td>0.5344</td>
<td>0.9238</td>
</tr>
<tr>
<td>LDL-cholesterol (mmol/L) median (min-max)</td>
<td>3.3 (1.0–7.3)</td>
<td>3.3 (1.0–6.3)</td>
<td>3.5 (1.4–6.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TG (mmol/L) mean ± SD</td>
<td>1.8 ± 1.1</td>
<td>1.9 ± 1.2</td>
<td>1.9 ± 1.3</td>
<td>0.9153</td>
<td>0.6101</td>
<td>0.4782</td>
</tr>
<tr>
<td>TG (mmol/L) median (min-max)</td>
<td>1.5 (0.4–9.9)</td>
<td>1.6 (0.6–10.7)</td>
<td>1.6 (0.6–10.9)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>35.9%</td>
<td>19.7%</td>
<td>23.7%</td>
<td>0.0248</td>
<td>0.4039</td>
<td>0.0024</td>
</tr>
<tr>
<td>Hypertension</td>
<td>65.3%</td>
<td>41.4%</td>
<td>59.2%</td>
<td>0.2982</td>
<td>0.0020</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Smoking habit</td>
<td>80.4%</td>
<td>77.1%</td>
<td>49.2%</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.5399</td>
</tr>
</tbody>
</table>

AAA = abdominal aortic aneurysm; AIOD = aortoiliac occlusive disease; BMI = body mass index; TG = triglycerides; AAA size = mean 61.5 mm ± 11.2 mm.

Table 2

Genotype Distribution and Allele Frequencies of the ACE Gene Polymorphism in all Studied Groups: AAA, AIOD, Control, and Population

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Allele</th>
<th>AAA (n = 133)</th>
<th>AIOD (n = 152)</th>
<th>Control (n = 152)</th>
<th>Population (n = 392)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>n %</td>
<td>n %</td>
<td>n %</td>
<td>n %</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td></td>
<td>27 20.3</td>
<td>34 22.4</td>
<td>30 19.7</td>
<td>104 26.5</td>
<td>n.s. a</td>
</tr>
<tr>
<td>ID</td>
<td></td>
<td>74 55.6</td>
<td>85 55.9</td>
<td>89 58.6</td>
<td>181 46.2</td>
<td>n.s. a</td>
</tr>
<tr>
<td>DD</td>
<td></td>
<td>32 24.1</td>
<td>33 21.7</td>
<td>33 21.7</td>
<td>107 27.3</td>
<td>n.s. a</td>
</tr>
<tr>
<td>I</td>
<td>0.481</td>
<td>0.503</td>
<td>0.490</td>
<td>0.496</td>
<td>0.496</td>
<td>n.s. a</td>
</tr>
<tr>
<td>D</td>
<td>0.519</td>
<td>0.497</td>
<td>0.510</td>
<td>0.504</td>
<td>0.504</td>
<td>n.s. a</td>
</tr>
</tbody>
</table>

AAA = abdominal aortic aneurysm; AIOD = aortoiliac occlusive disease.

* n.s.: non-significant both in dominant (DD + ID versus II) and recessive (DD versus ID + II) models of inheritance: AAA versus control; AIOD versus control; AAA versus population; AIOD versus population; control versus population.
(Table 3), significant differences were found in the dominant model of inheritance between hypertensive patients with AAA and normotensive patients with AAA (OR = 3.08 95% CI 1.22–7.79, P = 0.0147); and hypertensive patients with AAA and the population group (OR = 2.56 95% CI 1.27–5.16, P = 0.0066). Since majority of patients were males, similarly significant differences were found also between hypertensive men with AAA and normotensive men with AAA, hypertensive men with AAA and the population group and hypertensive men with AAA and male population group (data not shown). No relation of the ACE gene polymorphism to hypertension in the AIOD group was found (Table 3).

A multivariate analysis of the risk factors between the AAA and AIOD patients indicated hypertension and BMI as risk factors more significant for AAA than for AIOD. Patients with AAA were also significantly older than patients with AIOD (Table 4).

**DISCUSSION**

The present study examined the role of the ACE I/D gene polymorphism in susceptibility to the development of the AAA or AIOD. For the first time, we analyzed the ACE I/D gene polymorphism as a potential predisposing factor for two different pathological conditions sharing the same localization in abdominal aorta and common risk factors.

At the beginning of our study, the control group was recruited from healthy young volunteers, medical students of Poznan University of Medical Sciences, with no family history of vascular diseases. All subjects had levels of lipid fractions within reference limits. The ACE I/D genotype distribution and allele frequencies of the controls were compared with those of the AAA group or the AIOD group and no difference was found.

**TABLE 4**

**Multivariate Logistic Regression Analysis of Traditional Risk Factors and ACE Gene Polymorphism in the AAA versus AIOD Groups**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted* OR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.136</td>
<td>1.09–1.19</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Gender (male versus female)</td>
<td>1.82</td>
<td>0.74–4.48</td>
<td>0.1910</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.29</td>
<td>1.17–4.49</td>
<td>0.0148</td>
</tr>
<tr>
<td>Smoking habit</td>
<td>2.26</td>
<td>0.87–5.90</td>
<td>0.0924</td>
</tr>
<tr>
<td>BMI</td>
<td>1.11</td>
<td>1.02–1.20</td>
<td>0.0138</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>1.22</td>
<td>0.52–2.89</td>
<td>0.0644</td>
</tr>
<tr>
<td>Genotype DD + ID versus II</td>
<td>0.92</td>
<td>0.40–2.10</td>
<td>0.8420</td>
</tr>
</tbody>
</table>

* Adjusted for age, gender, hypertension, smoking habit, BMI, and dyslipidemia.

Note. Statistically significant: P-value < 0.05.
Statistically significant differences were detected only when hypertensive AAA patients were compared with the control group in dominant model of inheritance: $DD + ID$ versus $II$ (data not shown).

Since the optimum control group should be matched both by age and gender, we collected the control group described in the present study. The AAA onset usually occurs several years later than the onset of AIOD, therefore the mean age of patients with AAA was higher in comparison with that of the AIOD patients. Hence the mean age of controls was between that of the AAA and the AIOD groups. The controls were also comparable to the AAA and AIOD groups by the lipid fraction status except HDL-cholesterol. Since in preliminary investigations we observed differences only in the hypertensive AAA patients, in the present study the age-matched control group was deliberately composed of subjects with and without hypertension in proportion comparable to that of the AAA group. Consequently, some of the hypertensives in the control group had a history of MI, however all of them suffered from stable angina at the time of the study. In our opinion, that does not interfere with the results of the present investigation. The calculations of genotype distribution and allele frequencies were also performed on the control group excluding patients with MI history but it did not influence the results. Patients in the AAA and AIOD groups also included individuals with MI history, and the percentage of such individuals was the highest in the AAA group. The conflicting results concerning the correlation of $ACE$ gene polymorphism with MI were reported [9–11, 23, 24], and two meta-analyses of large scale studies excluded the $ACE I/D$ gene polymorphism as a risk factor for ischemic heart disease and MI [25, 26].

In our study, we did not confirm the association of $ACE I/D$ gene polymorphism with aortic abdominal aneurysm in normotensive patients reported by Pola et al. [19], and in both normotensive and hypertensive patients reported by Fatini et al. [20], compared with controls. However, the lack of significant differences between normotensive or hypertensive AAA patients and controls observed in our studies is in agreement with results of Hamano et al. [18]. It is noteworthy that in our study the control group was composed of atherosclerotic subjects who were more representative than healthy subjects, as in the studies by Fatini [20].

We observed significant increase of the $D$ allele frequency only in a dominant inheritance model in hypertensive AAA patients compared with normotensive AAA patients or the general population group. Since the majority of subjects were males, this correlation was also true when male hypertensive subjects (excluding females) with AAA were compared with male normotensive patients with AAA, to whole population group, or to male population group.

We performed many analyses to determine the potential association of the $ACE I/D$ polymorphism with hypertension in studied groups. No differences were observed when: hypertensive AAA patients were compared with hypertensive controls; or normotensive AAA patients were compared to normotensive controls; or hypertensive controls were compared to normotensive controls (Table 3). This showed that single event of having hypertension or having AAA was not associated with $D$ allele in studied groups. However, when hypertensive AAA patients were compared with normotensive control, we did not observe any difference in $D$ allele frequency. Since the allele frequencies were not significantly different in hypertensive AAA patients and hypertensive control subjects, it is difficult to argue that patients with hypertension are at greater risk for AAA if they have the $D$ allele. However, we observed an association between the presence of the $D$ allele in hypertensive AAA compared with normotensive AAA or to general population control, and no such associations were observed between hypertensive and normotensive AIOD patients and population control (Table 3). Our results indicate that it is possible that patients with the $D$ allele and hypertension are at greater risk for AAA than patients with the $D$ allele who do not have hypertension. The association between $ACE I/D$ gene polymorphism and essential hypertension is considered to be controversial [10, 11, 27, 28]; nonetheless the report of the Framingham Heart Study showed evidence for the association and genetic linkage of the $ACE$ locus with hypertension in men but not in women [29].

The differences in the results, concerning correlation of $ACE$ gene polymorphism with AAA, obtained by us on Polish subjects, and by Pola [19] and Fatini [20] on Italian patients, may be explained by several reasons. First, in the studies by Fatini et al. [20], the control group was not matched to AAA patients in relation to hypertension, dyslipidemia, and smoking. In studies by Pola et al. [19], the control was also not perfectly matched to the patients. It should also be considered that there may be different impact that polymorphism may have on populations with different genetic backgrounds and different diets. It is noteworthy that the genotype distribution of the $ACE I/D$ in Italy showed a clear, significant trend toward higher frequency of the $D$ allele in the southern part of Italy (0.670) compared with northern regions (0.610) [30], whereas in Poland, we found it as 0.504 (Table 2). The epidemiology of essential hypertension is comparable in both countries. In Italy, the overall rate of hypertension was established as 37.7% [31]. In Poland, the recent large scale studies WOBASZ [32] determined the frequency of hypertension in Polish population as 36.0%. No association of $ACE I/D$ polymorphism with hypertension was observed in Italian studies [30].
We found that there is no correlation between ACE I/D polymorphism and AIOD independently of the blood pressure status. Since we do not know any published data regarding ACE I/D polymorphism in AIOD, we can compare our results with the studies concerning peripheral arterial disease and ACE polymorphism reporting lack of such correlation [33, 34]. However, the results concerning association of cardiac and carotid atherosclerosis with ACE I/D gene polymorphism remain controversial [11, 35].

The atherosclerotic process is considered to be a systemic disease; however it affects various regions of the circulation preferentially. Thus it yields distinct clinical manifestations depending on the particular circulatory bed affected. The mechanisms underlying this discontinuous anatomical distribution of atherosclerosis remain largely uncertain. The ACE I/D gene polymorphism may contribute to these mechanisms but other polymorphisms of the ACE gene may be also involved [11].

The comparison of the classic risk factors by multivariate analysis as conducted in our study indicated hypertension, BMI, and age as risk factors more significant for AAA than for AIOD. The finding that hypertension is a stronger predisposing factor to AAA may be supportive to the association discussed above between the ACE genotype and occurrence of AAA only in hypertensive AAA patients. The importance of age factor is supported by fact that AAA onset is usually several years later than onset of AIOD. Although aortic abdominal aneurysms most often arise in association with atherosclerosis, significant evidence from many different perspectives suggests that atheroma and occlusive atherosclerosis are two different pathological processes [1] that may also explain our results.

Some limitations should be considered in this study. The control group has not been matched precisely for age and smoking habit to the AAA group or AIOD group. The mean age of controls was lower from the AAA patients and higher from the AIOD patients. The mean age of general population group was lower from AAA patients and higher from AIOD patients. The comparison of the classic risk factors by multivariate analysis as conducted in our study indicated hypertension, BMI, and age as risk factors more significant for AAA than for AIOD. The finding that hypertension is a stronger predisposing factor to AAA may be supportive to the association discussed above between the ACE genotype and occurrence of AAA only in hypertensive AAA patients. The importance of age factor is supported by fact that AAA onset is usually several years later than onset of AIOD. Although aortic abdominal aneurysms most often arise in association with atherosclerosis, significant evidence from many different perspectives suggests that atheroma and occlusive atherosclerosis are two different pathological processes [1] that may also explain our results.

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In conclusion, this study shows that ACE I/D gene polymorphism is not a susceptibility factor to aortoiliac occlusive disease; however, it may be an important factor in development of AAA when coexisting with hypertension. We consider that it is possible that patients with the D allele and hypertension are at greater risk for AAA than patients with the D allele who do not have hypertension; however, further studies will be needed to confirm the relationship of the I/D ACE gene polymorphism, hypertension, and AAAs. Also, future studies on the comparison of the potential association between ACE I/D gene polymorphisms (or other polymorphisms of the ACE gene) and AAA or AIOD in other populations, considering environmental factors, especially in the context of benefits of treatment with ACE inhibitors, would be worthwhile.

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